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We salute Schering Corporation for their contribution to the Endowment Fund and for their continued support of clinical and investigative dermatology.

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In This Issue . . .

Selective Retinoid Receptor Agonists: Tools to Understand the Function of Retinoid Receptors

Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) are nuclear receptors that mediate the wide-ranging biologic effects of retinoids. (The retinoid that binds to RXR receptors was originally not known but is now known to be 9-cis-retinoic acid). These receptors are transcription factors that affect gene expression by binding to critical regions of DNA capable of initiating gene expression after the receptors are activated by retinoids. RARs and RXRs can combine to form a heterodimeric complex (RAR/RXR) that binds to target genes, and RXRs, unlike RARs can form homodimers (RXR/RXR). Unlike RXR/RAR heterodimers, however, RXR/RXR homodimers can only form in the presence of retinoids.

One way to study the function of these two types of receptors is to use compounds that bind to either RARs or RXRs but not to both. This is similar to the approach used by investigators at CIRD Galderma to show that RARs and not cellular retinoic acid-binding protein (CRABP) are required for the effects of retinoids on keratinocyte differentiation (*J Invest Dermatol* 98:128–134, 1992). All trans-retinoic acid and its stereoisomer, 9-cis-retinoic acid, activate RXR/RAR heterodimers. RXR/RXR homodimers are induced and activated by 9-cis-retinoic acid or by a synthetic compound, SR11237. But unlike 9-cis-retinoic acid, SR11237 is selective and does not activate RXR/RAR heterodimers. In this issue, Gendimenico *et al* (p. 676) report their results using the selective ligand, SR11237. First, they confirmed in their own experimental system the findings of Magnus Pfahl and Marcia Dawson (*Science* 258:1944–1946, 1992) that SR11237 activates RXR but not RAR. In studies of the biologic effects of these retinoids, they found that a complex biologic response induced by all-trans-retinoic acid in F9 embryonal cells and in rhino mouse skin could not be produced by SR11237. (F9 cells and mouse skin constitutively express both RARs and RXRs.) These studies suggest that RXR/RAR heterodimers, not RXR/RXR homodimers, are responsible for this classical pleiotropic response of retinoids in biologic systems. These studies help delineate what kind of responses are produced by each retinoid. Such knowledge is critical in understanding how to target new retinoids to specific biologic pathways.

Molecular Heterogeneity in Hepatoerythropoietic Porphyria

Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive disorder that produces severe photosensitivity and is caused by a homozygous deficiency of uroporphyrinogen decarboxylase (UROD), an enzyme in the heme biosynthetic pathway that converts uroporphyrinogen into coproporphyrinogen. It is known that there are striking differences in UROD deficiency in different patients with the disorder. Some patients with UROD deficiency have immunologically undetectable enzyme, but in others it is detectable but inactive, and these different clinical types of UROD deficiency have been found to have different mutations. (For a description of "cross reactive material" (CRM) positive and negative UROD mutations, see Kappas *et al* in *The Metabolic Basis of Inherited Disease,* Scriver *et al* (eds.). McGraw-Hill Book Co., 1989, pp 1305–1365). In this issue, Meguro *et al* (p. 681) report molecular analysis of UROD in yet another type of HEP, involving a CRM "supernegative" mutation. The patient studied had a unique discrepancy, a significant amount of UROD activity (~20% normal) but an immunologically undetectable amount of enzyme protein in his erythrocytes. To elucidate the UROD defect, the authors cloned UROD DNAs from the patient's cells, and analyzed their nucleotide sequences. They found that the patient had two separate missense mutations in each of his two UROD alleles; that is, the proband is a *compound heterozygote* for the UROD defect. One mutation was a single base transition resulting in a $His^{220} \rightarrow Pro$ change, whereas the other comprised three successive point mutations (TGT → CCA), but resulted only in a $Val^{134} \rightarrow Gln$ change. Despite the mutation, these mutant UROD cDNAs produced significant enzyme activity when they were transfected into Chinese hamster ovary cells and expressed, consistent with the authors' finding of significant UROD activity in the proband's erythrocytes. With this report, six different mutations have been described to date in four different families with HEP (Table 1, p. 684), suggesting a marked heterogeneity of UROD deficiency in this disorder. It is also interesting to note that none of the mutations found in UROD deficiency in HEP has been reported in patients with familial porphyria cutanea tarda (fPCT), which is caused by heterozygous UROD deficiency, raising the possibility that HEP is not a homozygous form of fPCT.

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How to Interpret Immunofluorescence Studies with Pemphigoid Sera

The 230-kDa and 180-kDa bullous pemphgoid (BP) antigens, prominent components of the cutaneous basement membrane, are defined immunologically by autoantibodies in the sera of patients with the supepidermal blistering disease BP. Biochemical and molecular biologic studies have shown that BP antigen (BPAG) is composed of two major hemidesmosome-associated proteins, the 230-kDa antigen (BPAG1) and the 180-KDa antigen (BPAG2). Recent immunoelectron microscopic studies showed that BPAG1 is an intracellular protein, whereas BPAG2 is a transmembrane protein and can be detected on the cell surface (Ishiko *et al: J Clin Invest* 91:1608–1615, 1993).

Rather than immunoelectron microscopy, which is a demanding technique and is available only in a few laboratories, antigenic mapping using skin "split" after prolonged incubation in buffers containing 1 M NaCl has been used extensively to characterize the binding site of BP autoantibody, especially to distinguish patients with other blistering disorders such as epidermolysis bullosa acquisita and bullous systemic lupus erythematosus. When human skin is incubated with 1 M NaCl, the basement membrane splits at the lamina lucida. Most BP sera bind only to the epidermal side of this split skin, but some sera from patients classified as having BP bind to the dermal side as well. The relationship between autoantibodies identifying BPAG1 or BPAG2 or both and their binding sites on 1 M NaCl split skin has not been elucidated. In this issue, Yuko Onodera and her colleagues from Keio University in Tokyo (p. 686) studied more than 100 BP sera by immunofluorescence on split skin, immunoblotting, and immunoelectron microscropy. Their studies show that sera containing autoantibodies against BPAG1 or BPAG2 or both antigens always decorate the epidermal side of split skin and never bind solely to the dermal side. They also demonstrate that autoantibodies against BPAG2, but not those against BPAG1, bind both epidermal and dermal sides of split skin. They speculate that although BPAG1 is always found on the epidermal side in split skin, BPAG2 may be present on both epidermal and dermal sides. These results should provide a better conceptual basis for the interpretation of the binding pattern of pemphigoid serum on split skin.

Abnormal Keratin Filaments in Epidermolytic Hyperkeratosis *In Vitro*

Epidermolytic hyperkeratosis (EHK), an autosomal dominant skin disorder characterized by erythematous blisters early in life and hyperkeratosis later, shows characteristic ultrastructural abnormalities in the epidermis. The most prominent feature is collapse of the keratin intermediate filament network composed of keratins 1 and 10 (K1 and K10), which produces clumped and perinuclear tonofilaments on electron microscopy. Data from linkage studies are in agreement with nucleotide sequence analyses of DNA strongly suggesting that point mutations in the K1 or K10 genes are responsible for the EHK phenotype. In this issue, Huber *et al* (p. 691) describe the cytoskeleton of keratinocytes cultured from two EHK patients with mutations in the K10 1A rod domain. When they proliferate, the EHK keratinocytes express K5 and K14 and have a normal cytoskeleton. When they differentiate, however, and express K1 and K10, the morphology becomes abnormal. The authors show that the mRNA expressed in these cells reflects the mutations found in the patient's genomic DNA, and immunofluorescence with anti-K1 and anti-K10 antibodies shows changes similar to those found in EHK keratinocytes *in vivo*. These results indicate that changes in the rod domain 1A of K10 are responsible for morphologic changes *in vitro* comparable to those found *in vivo*, a finding similar to that in epidermolysis bullosa simplex, in which mutations in the rod domains of K5 and K14 have been described (see the review by Fuchs E: *J Invest Dermatol* 99:671–674, 1992). Although two K10 point mutations in EHK patients have now been clearly linked to the collapse of the intermediate filament network, it will be important to determine how the mutation produces blisters in infancy and hyperkeratosis later in life.

Identification of the Risk of Melanoma

Moles, skin type and hair color, and sunburns in childhood have been proposed as risk factors for melanoma, but the role of moles is controversial. R. Mackie *et al* have calculated risk based on total number of nevi, the number of atypical melanocytic nevi, a freckling tendency, and episodes of sunburn (*Lancet* II:487–490, 1989). In this issue, Garbe *et al* (p. 695) describe a prospective multicenter study of 513 newly diagnosed melanoma patients and 498 controls. All subjects were examined by dermatologists for common and atypical nevi, actinic lentigines, other types of pigmented lesions, pigmentation, and solar damage. Interviews were used to determine sun exposure, sunburns, and other possible risk factors. Multivariate regression analysis revealed six independent factors with significant impact on risk: common melanocytic nevi, atypical melanocytic nevi, actinic lentigines, hair color, skin type, and reported growth of melanocytic nevi. Sunburn in childhood, found to be a significant risk factor by bivariate analysis, was excluded from the independent factors after adjustment for other risk factors. The most important factors were the total number of common melanocytic nevi and the number of atypical melanocytic nevi, which showed 7.6-fold and 6.1-fold risks for developing melanoma. The increase in risk was nearly linear with increasing number of common melanocytic nevi. Only a slightly increased risk increase was found for one to four atypical melanocytic nevi, but a marked increase was found for five or more such nevi. These findings suggest that clinical recognition of atypical nevi without histologic examination can identify patients with increased risk for melanoma and that a threshold value exists for defining the syndrome of atypical nevi. High numbers of common melanocytic nevi, presence of atypical melanocytic nevi, and presence of actinic lentigines distinguished subgroups with relative risks ranging from 1 to 121. With these results, and using the proposed risk assessment scheme, the authors feel that dermatologists should be able to recognize persons at increased risk for melanoma by examination alone.